Chapter 4: Health Effects of PCBs

I. Introduction

This chapter focuses on epidemiological evidence for neurotoxicity as a result of developmental exposure to PCBs, rather than on experimental studies. Neurotoxicity has been identified in a number of longitudinal prospective cohort studies as a consequence of environmental exposure to PCBs. These studies allow an estimation of the maternal body burden of PCBs in humans that may result in adverse effects, and are therefore potentially suitable for developing a fish consumption advisory.

Section II outlines the toxicological basis for current advisories in various states. Section III provides a review of results from epidemiological studies on the behavioral effects of developmental PCB exposure. Section IV discusses the body burden of PCBs in the epidemiological studies, and a comparison to effects in the general U.S. population. Section V describes the state of knowledge concerning the relative toxicity of specific PCB congeners, including data from epidemiological and experimental studies. Section VI discusses the information available on the shape of the relationship between body burden and adverse effect, including evidence of a threshold. Finally, Section VII proposes approaches for derivation of a fish advisory based on PCB body burdens, as well as the more standard reliance on a toxicity value derived by a federal agency.

II. Current Bases for PCB Fish Advisories

The toxicological basis for east coast state fish consumption advisories based on PCB concentrations in fish varies among the states. Toxicological bases include application of EPA's cancer slope factor for PCBs, EPA's reference dose (RfD) for Aroclor 1254 or 1016, the Great Lakes Health Protective Value (HPV) from the Great Lakes Protocol, or the FDA tolerance level. Each of these approaches is briefly described.

A. EPA RfD for Aroclor 1254 and 1016

Derivation of these RfDs is presented on EPA's IRIS Web site under "Aroclor". The RfDs for Aroclor 1254 and Aoclor 1016 both represent testing on commercial mixtures, and do not necessarily correspond to the PCB congener patterns typically present in foods or in humans following environmental exposure. Of the two, food and human tissue patterns are typically closer to the congeners found in 1254 than 1016.

The oral RfD for Aroclor 1254 of 2E-5 mg/kg/day was derived in 1996 based on studies published in 1989-1993. The lowest observed adverse effect level (LOAEL) of 5E-3 mg/kg/day in adult female rhesus monkeys was based on inflamed Meibomian glands, changes in fingernail beds, and effects on several immune parameters. Uncertainty factors (UFs) applied to derive the RfD included a factor of 3 for use of a LOAEL, a factor of 3 for interspecies extrapolation, a factor of 10 for inter-individual variability, and a factor of 3 for use of a subchronic (55 months) rather than a chronic study (cumulative UF = 300 fold).

The oral RfD for Aroclor 1016 of 7E-5 mg/kg/day was derived in 1996 based on studies published in 1984-1991. The no observed adverse effect level (NOAEL) of 7E-3 mg/kg/day

was identified for reduced birth weight in rhesus monkeys. Mothers were exposed to Aroclor 1016 beginning 7 months before initiation of breeding, and infants were weaned at 4 months of age. UFs applied to the NOAEL included a factor of 3 for interspecies extrapolation, a factor of 3 for database insufficiency, a factor of 3 for use of a subchronic study, and a factor of 3 for inter-individual variability.

B. EPA Cancer Slope Factor

PCBs are classified by EPA as a "probable human carcinogen" (B2). Slope factors (SFs) for PCBs are presented on the IRIS Web site under "polychlorinated biphenyls". The SFs are based on carcinogen bioassays in rats with Aroclors 1260, 1254, 1242, and 1016. The lower chlorinated formulations, Aroclor 1242 and 1016, were less potent than 1260 and 1254. An upper bound CSF of 2.0 mg/kg/day was recommended for high-risk and persistent mixtures. This SF is used by the states that rely on the cancer endpoint to set advisories, presumably because the higher chlorinated congeners predominate in fish.

C. Great Lakes Health Protective Value

In the early 1990s, representatives of the Great Lakes states convened a task force to develop a framework for risk-based fish consumption advisories. The resultant document, "Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory", included a risk assessment for PCBs in fish (GLSFATF, 1993). A weight-of-evidence approach was used to derive a Health Protective Value (HPV) of 5E-5 mg/kg/day based on monkey (immunological and endocrine) and human (developmental) effects. This risk assessment attempts to construct a dose-response relationship from human neurodevelopmental data, using the Michigan Maternal Infant Cohort Study. A LOAEL 5E-4 mg/kg/day was estimated for decreased gestational age and head circumference (Tilson *et al*., 1990; Minnesota DOH, 1992). This assessment related postnatal effects to maternal dose via maternal body burden (converted to daily intake rate using toxicokinetic assumptions) and based on a fish consumption survey.

D. FDA Tolerance Level

The FDA Tolerance Level for PCBs in fish was derived in 1982 (Cordle *et al*., 1982), from an FDA-derived acceptable intake of 0.001 mg/kg/day based on an episode of poisoning in Japan, referred to as the Yusho incident. This episode resulted in overt and serious health effects, including neurological symptoms, chloracne, and disturbances in liver function. Offspring of exposed women had decreased IQ (in the mentally retarded range for some individuals) as well as overt signs of toxicity. The FDA applied a total UF of only 10 to these serious effects, which is a questionable health-protective strategy. Typically, UFs would be applied to go from a LOAEL to a NOAEL, and for inter-individual variability. Default values are usually a factor of 10 unless there are data available that support a lower value.

III. Epidemiological Studies of Neuropsychological Effects of PCBs in Children

It became clear from episodes of human poisoning in Japan and Taiwan that the fetus was more sensitive to the effects of PCBs than the adult (see Schantz *et al*., 2003 for review). In the poisoning episodes, babies were born with hyperpigmented skin, orbital edema, gingival hyperplasia, natal teeth, abnormal calcification of the skull, and hypersecretion of the Meibomian glands. Severely affected children were mentally retarded and had other neurological

impairments. Follow-up studies of the Taiwan cohort identified lowered IQ, sensory abnormalities, and emotional problems.

These episodes of human poisoning prompted exploration of the consequences of environmental exposure to PCBs. Several longitudinal prospective studies have assessed the effects of PCB exposure on developmental neuropsychological function in children as a consequence of prenatal and/or postnatal exposure to PCBs (see Schantz *et al*., 2003 and Rice, 2006, for reviews). Neuropsychological deficits that persisted to the latest ages measured were documented as a consequence of pre- or post-natal PCB exposure. These studies are all high-quality studies, with good covariate control.

Current toxicity values are based on data from studies that are one to two decades old, and rely on animal studies or initial results from the first epidemiological study. The more recent data from several epidemiological studies would provide a more appropriate basis of a noncancer RfD for PCBs than would the animal studies currently used.

A. Michigan Study

A study was initiated in the 1980s in which women who did or did not eat Lake Michigan fish were recruited, and their offspring assessed at various ages from infancy to 11 years, with about 250-325 children were assessed at various ages (Table 1). The analytical methodology used in this study for detection of PCBs was less sensitive and precise than methods currently available. PCB analysis was performed by packed-column gas chromatography, adapting the Webb-McCall method. Aroclors 1016 and 1260 were used as reference standards. The concentrations of specific congeners could not be determined by this method, and this method would result in measurement error because the pattern of congeners in human tissue does not match commercial mixtures; this could potentially lead to exposure misclassification. PCB concentrations were measured in cord and maternal blood and breast milk. Duration of breast feeding and fish consumption were also ascertained. Over two-thirds of the cord blood samples and 22% of the maternal blood samples were below the analytical detection limit attained in the study. For some analyses of endpoints at four and 11 years, a composite of maternal and cord blood and milk PCB levels was used as the measure of prenatal exposure to address this problem.

Table 1. Summary of Identified Associations Between PCB Exposure and Adverse Neuropsychological Effects

	Michigan	Oswego	The Netherlands	Germany	Faroe Islands
Study population	eaters and non-eaters of Lake Michgan fish	eaters and non-eaters of Lake Ontario fish	general population, half breast-fed, half not	general population	fish- and whale-consuming population
Number of subjects	325	309	418	171	450 with PCB levels
PCB analysis	packed-column GC, Aroclors 1016 and 1260 as references	cord blood: 68 congeners or congener pairs	cord and maternal blood: 118, 158, 153, 180 breast milk in breast-feeding mothers: 118, 138, 153, 180; 17 dioxins and furans; 6 dioxin-like and 20 ortho-substituted PCB congeners	cord and maternal blood, breast milk: 138, 153, 180	cord tissue: 138, 153, 180
Infant neurological status	NBAS: abnormal responses (based on fish consumption)	NBAS: abnormal responses	Precchtl neurological exam: abnormal responses	np	np
Fagan test of recognition memory	impaired: lower preference for novel stimulus	impaired: lower preference for novel stimulus	np	no effect	np
Bayley Scales of Infant Development	no effect	np	PDI: lower score MDI: no effect	MDI: lower score PDI: no effect	np
Cognitive effects 3–4 years	McCarthy: lower IQ	McCarthy: lower IQ	K-ABC: lower IQ	K-ABC: lower IQ	np
Cognitive effects 4–7 years	np	McCarthy: no effect on IQ	McCarthy: lower IQ in less-advantaged children	K-ABC: non-significant negative effect on IQ	Bender Gestalt: no effect WISC-R (3 subtests): no effect
Cognitive effects in later childhood	WISC-R, 11 years: decreased full-scale and verbal IQ	np	Tower of London, 9 years: poorer performance Rey Complex Figure Test: no effect	np	np

Attention/response inibition/processing speed	vigilance task: increased errors of commission freedom from distractibility WISC-R: impaired Wisconsin Card Sort: increased perseverative errors mental rotation task: slower reaction time	vigilance task: increased errors of commission	vigilance task: increased errors simple reaction time: impaired	np	vigilance task: no effect after control for mercury
Language	Woodcock Reading Mastery Test word comprehension: impaired WISC-R reading comprehension, verbal comprehension: impaired	np	Reynell Language Development Scale: impaired performance	np	Boston Naming Test: no effect after control for mercury California Verbal Learning Test: no effect
Memory	WISC-R vocabulary and information scores: impaired	np	Auditory Verbal Learning Task: no effect	np	np
Social Behavior	np	np	CBCL: increased abnormal scores	np	np
Activity	rating scale: decreased activity	np	rating scale: increased activity play behavior: sexually dimorphic differences	np	np

np = not performed

Covariates included SES, maternal IQ, HOME score, maternal education, parity, maternal drinking and smoking during pregnancy, and other measures of the child's environment. Concentrations of lead, PBBs, DDT, and seven pesticides were measured at 4 years. Of the pesticides, only DDT was detected. Body burden of methylmercury was not measured.

Prenatal PCB exposure was associated with lower birth weight, smaller head circumference, and shorter gestational age (Fein *et al*., 1984). Decreased weight persisted at least until four years of age (Jacobson *et al*., 1990b). Maternal fish consumption was associated with motoric immaturity, poorer lability of states, abnormal reflexes, and a greater degree of startle on the Neonatal Behavioral Assessment Scale (NBAS) during infancy (Jacobson *et al*., 1984). Neither fish consumption nor cord serum PCB concentration was associated with performance on the Bayley Scales at 5 and 7 months (Jacobson and Jacobson, 1986), but a deficit on the Fagan Test of Recognition Memory was associated with cord PCB levels (Jacobson *et al*., 1985). At four years of age, breast milk and cord PCB levels were associated with poorer performance on the McCarthy Scales for verbal and numeric memory (Jacobson *et al*., 1990a). Prenatal exposure was also related to poorer short-term memory and increased reaction time on a visual discrimination task (Jacobson *et al*., 1992). A decreased number correct responses and increased errors of commission were observed at four years of age on the Sternberg Memory paradigm, a computerized test of working memory that allows responding to digits not on a sample list (Jacobson and Jacobson, 2003a). The child's concurrent PCB blood concentration was associated with reduced activity at four years (Jacobson *et al*., 1990b).

The Michigan cohort was assessed for a final time at 11 years of age. Prenatal exposure was associated with decreased full-scale and verbal IQ on the WISC-R, particularly with memory and attention subscales (Jacobson and Jacobson, 1996). Prenatal PCB exposure was also associated with poorer word comprehension and overall reading comprehension. The most highly exposed children (children whose prenatal PCB exposure equivalent was estimated to be at least 1.25 ug/g milk fat, 4.7 ng/g cord serum, or 9.7 ng/g maternal serum) were more than three times more likely to score one standard deviation below the mean for full-scale IQ and twice as likely to be at least two years behind in reading. The most highly exposed children averaged 6.2 points lower in IQ than children less exposed. Prenatal PCB exposure was also associated with increased perseverative errors on the Wisconsin Card Sort test, deficits in attention on the Digit Cancellation task, slower reaction time on a mental rotation task, and increased errors of commission on a vigilance test at 11 years (Jacobson and Jacobson, 2003b). These results are indicative of problems with executive function.

In a re-examination of the effects at 4 and 11 years (Jacobson and Jacobson, 2002), investigators reported a decrease in IQ at four and 11 years in infants breast-fed fewer than 6 weeks, but not those breast-fed more than 6 weeks (Jacobson and Jacobson, 1992). These results could be accounted for statistically by quality of parental intellectual input, with adverse effects strongest in children of less verbally competent mothers (Jacobson and Jacobson, 2002a; Jacobson *et al*., 1999). The findings in these studies are consistent with studies in lead-exposed children, in which adverse effects were greater in less advantaged children (Bellinger, 2000). It appears that high-quality parental care may ameliorate, or at least attenuate, the effects of neurotoxic agents. Effects were observed on nine of 21 outcome measures in infants breast-fed fewer than six weeks, and on two different measures in infants breast-fed more than six weeks

(Jacobson and Jacobson, 2003b). These latter effects (reaction time on a mental rotation task and errors on the Seashore Rhythm test) may be chance findings, or may reflect an influence of postnatal exposure.

B. Oswego Study

The Oswego longitudinal prospective study included women recruited from 1991-1994 who did or did not consume Lake Ontario fish. A total of 309 offspring were assessed during infancy and childhood. Sixty-eight congeners or congener pairs were measured in cord blood, with no analysis of maternal blood (Stewart *et al*., 1999). Breast milk was analyzed from a subset of women at varying times during the first six months following delivery, thereby essentially obviating the possibility of assessing any effects of postnatal exposure via breast milk.

Covariables included maternal and paternal education and physical characteristics (age, height, weight, etc.); maternal IQ and performance on relevant tasks assessed in the children; HOME score; pregnancy and birth weight; head circumference; illicit and licit drug use, smoking, alcohol consumption, and caffeine intake during pregnancy; and several other health and demographic variables of the family. Cord blood concentrations of DDE, mirex, and hexachlorobenzene were also measured, as well as maternal hair mercury and blood lead concentration of the child. These contaminants were not directly related to performance on any measure.

Fish consumption was predictive of the concentration of the most highly chlorinated PCB congeners (Cl 7-9), but not the lower chlorinated homologs (Cl 1-3 or 4-6). Overall PCB levels in fish-eaters and non-fish-eaters were not different (P. Stewart, personal communication). Maternal intake of Lake Ontario fish or highly chlorinated PCBs predicted poorer performance on the NBAS at 6 and 12 months (Lonky *et al*., 1996; Stewart *et al*., 2000), similar to results in the Michigan study. Decreased fixation time for the novel stimulus on the Fagan Test of Recognition Memory was associated with highly chlorinated PCBs at 6 but not 12 months (Darville *et al*., 2000); this test was also affected in the Michigan study. IQ was assessed on the McCarthy Scales at 38 and 54 months of age (Stewart *et al*., 2003b). Effects were observed at 38 but not 54 months after covariate control; an interaction between PCBs and mercury was observed at 38 months.

Performance on a vigilance task was assessed in the Oswego study at 4.5 years of age (Stewart *et al*., 2003a). As in the Michigan study, increased errors of commission (failure of response inhibition) were related to *in utero* PCB exposure. In addition, an interaction was found between the size of the corpus collosum (a major brain fiber tract subserving interhemispheric communication) and increased PCB body burden on errors of commission; children with smaller corpus collosums were more impaired by increased PCB exposure. Children in this cohort were reassessed on a vigilance task at 8.0 and 9.5 years of age, to explore the behavioral mechanism responsible for the poor performance associated with PCB exposure (Stewart *et al*., 2005). Manipulation of schedule parameters indicated that failure of response inhibition rather than impairment of sustained attention was responsible for the performance deficit. As in the Michigan cohort, the results of these latter tasks are indicative of deficits in executive function that persisted to later ages.

C. Dutch Study

A study in the Netherlands was designed to assess the relative contribution of PCB and dioxin exposure *in utero* versus through breast milk on neuropsychological functions. Exposure was through the general food supply. A total of 418 mother-infant pairs were recruited from two cities, Rotterdam and Gröningen, in 1990–1992, with half the women in each city planning to breast-feed for at least 6 weeks and half not planning to breast feed.

The Dutch investigators measured, in both maternal and cord blood, the four congeners that typically are found at the highest concentrations in human tissue (congeners 118, 138, 153, and 180) (Koopman-Esseboom *et al*., 1996) (Table 2). They also measured 17 dioxins and furans, 6 coplanar or mono-ortho coplanar (dioxin-like) PCB congeners, and 20 ortho-substituted congeners in breast milk shortly after birth from the half of the mothers who breast-fed their infants. PCBs and other lipid-soluble chemicals are at higher concentrations in milk than blood, so that sampling of breast milk allowed analysis of more congeners with greater accuracy. The dioxins, furans, and dioxin-like congeners were used to calculate dioxin TEQs separately, or as a total TEQ. This provided the opportunity to determine the association between performance and concentrations of dioxins, dioxin-like- and non-dioxin-like PCBs in breast-fed infants, as well as the sum of the four congeners in maternal and cord blood and breast milk in the full cohort. Covariates included gestational length, birth weight, parity, parental IQ, HOME score, and alcohol use and smoking during pregnancy. Other contaminants were not measured.

Table 2. PCB congeners, dioxins, and furans analyzed in the Dutch study (from Schantz *et al*., 2003)

Exposure variable, IUPAC no.	Chorine substitution pattern	Number of subjects	Mean tissue level	Mean TEQ
ΣPCBs in maternal plasma				
118 138 153 180	2,3´,4,4´,5 2,2´,3,4,4´,5´ 2,2´,4,4´,5,5´ 2,2´,3,4,4´,5,5´	415 415 415 415 ΣPCBs = 2.21 ng/g	0.16 ng/g 0.60 ng/g 0.91 ng/g 0.54 ng/g	
ΣPCBs in cord blood				
118 138 153 180	2,3´,4,4´,5 2,2´,3,4,4´,5´ 2,2´,4,4´,5,5´ 2,2´,3,4,4´,5,5´	373 382 382 382	0.04 ng/g 0.13 ng/g 0.18 ng/g 0.10 ng/g ΣPCBs = 0.45 ng/g	
ΣPCBs in breast milk ng/g fat				
118 138 153 180	2,3´,4,4´,5 2,2´,3,4,4´,5´ 2,2´,4,4´,5,5´ 2,2´,3,4,4´,5,5´	195 195 195 195	35.5 ng/g 129.9 ng/g 186.3 ng/g 76.8 ng/g ΣPCBs = 428.5	3.6 0.8
Nondioxin-like PCBs measured in breast milk ng/g fat				
28 52	2,4,4´ 2,2´,5,5´	195 195	12.1 ng/g 2.6 ng/g	

66 70 99 101 128 137 138 141 151 153 177 183 187 194 195 202	2,3´,4,4´ 2,3´,4´,5 2,2´,4,4´,5 2,2´,4,5,5´ 2,2´,3,3´,4,4´ 2,2´,3,4,4´,5 2,2´,3,4,4´,5´ 2,2´,3,4,5,5´ 2,2´,3,5,5´,6 2,2´,4,4´,5,5´ 2,2´,3,3´,4´,5,6 2,2´,3,4,4´,5´,6 2,2´,3,4´,5,5´,6 2,2´,3,3´,4,4´,5,5´ 2,2´,3,3´,4,4´,5,6 2,2´,3,3´,5,5´,6,6´	195 195 195 195 195 195 195 195 195 195 195 195 195 195 195 195	11.6 ng/g 18.5 ng/g 19.7 ng/g 1.5 ng/g 4.0 ng/g 16.8 ng/g 129.9 ng/g 1.1 ng/g 0.9 ng/g 186.3 ng/g 6.3 ng/g 12.2 ng/g 20.0 ng/g 8.6 ng/g 2.9 ng/g 0.9 ng/g ΣPCBs = 455.9 ng/g	
Mono-ortho PCBs in breast milk ng/g fat				
105 118 156	2,3,3´,4,4´ 2,3´,4,4´,5 2,3,3´,4,4´,5	195 195 195	9.4 ng/g 35.5 ng/g 21.0 ng/g ΣPCBs = 65.9 ng/g	0.9 3.6 10.5 Σ TEQ = 15.0
Di-ortho PCBs in breast milk ng/g fat				
170 180	2,2´,3,3´,4,4´,5 2,2´,3,4,4´,5,5´	195 195	37.1 ng/g 76.8 ng/g ΣPCBs = 113.9 ng/g	3.7 0.8 ΣTEQ = 4.5
Planar PCBs in breast milk ng/g fat				
77 126 169	3,3´,4,4´ 3,3´,4,4´,5 3,3´,4,4´,5,5´	194 194 194	0.0193 ng/g 0.152 ng/g 0.0843 ng/g ΣPCBs = 0.2556 ng/g	0.01 15.2 0.8 ΣTEQ = 16.0
Dioxins in breast milk				
48 54 66 67 70 73 75	2,3,7,8 1,2,3,7,8 1,2,3,4,7,8 1,2,3,6,7,8 1,2,3,7,8,9 1,2,3,4,6,7,8 1,2,3,4,6,7,8,9	176 176 176 176 176 176 176	0.004 ng/g 0.0106 ng/g 0.0087 ng/g 0.0474 ng/g 0.0067 ng/g 0.0632 ng/g 0.7996 ng/g Σ Dioxins = 0.9402 ng/g	4.0 5.3 0.9 4.7 0.7 0.6 0.8 Σ TEQ = 17.0
Furans in breast milk				
83 94 114 118 121 130 124 131 134 135	2,3,7,8 1,2,3,7,8 2,3,4,7,8 1,2,3,4,7,8 1,2,3,6,7,8 2,3,4,6,7,8 1,2,3,7,8,9 1,2,3,4,6,7,8 1,2,3,4,7,8,9 1,2,3,4,6,7,8,9	176 176 176 176 176 176 176 176 176 176	0.0008 ng/g 0.0003 ng/g 0.0227 ng/g 0.0066 ng/g 0.0057 ng/g 0.0036 ng/g 0.0003 ng/g 0.0079 ng/g 0.0002 ng/g 0.0022 ng/g	0.08 0.01 11.3 0.7 0.6 0.4 0.03 0.08 0.0 0.0

			Σ Furans 0.0505 ng/g	Σ TEQ = 13.2 Total dioxin Σ TEQ = 65.7

Infants were assessed on the Prechtl neurological exam between 10 and 21 days after birth (Huisman *et al*., 1995a), which measures postural tone and reflexes. PCBs in maternal milk and total TEQ were related to poorer performance, whereas PCB levels in maternal or cord blood were unrelated (Table 3). Maternal blood PCB concentration was negatively associated with performance on the Bayley psychomotor development index (PDI) at three months. In contrast, postnatal TEQ, but not measures of prenatal exposure, was associated with poorer performance on the Bayley PDI at seven months, negating the positive effects of breastfeeding at higher exposures (Koopman-Esseboom *et al*., 1996). No effects of PCB exposure were observed on the Bayley Scales at 18 months, and no effects on the Bayley mental development index (MDI) were observed at 3 or 7 months. Maternal or cord blood PCB concentrations predicted poorer neurological status at 18 months of age (Huisman *et al*., 1995b).

Table 3. Neuropsychological effects of the Dutch study to 3.5 years of age (from Schantz *et al*., 2003)

Test	Age (months)	Outcome	Exposure	ΣPCB in cord blood	ΣPCB in maternal blood	ΣPCB in milk	Total dioxin/ PCB TEQs	References
Birth size and growth								Patandin et al. (1998)
Birth weight	0	↓	BF + FF	p = 0.03 (179)	p = 0.057 (203)			
Length	0.3	—	BF + FF	NS	NS			
Head circumference	3	—	BF + FF	NS	NS			
Prechtl's neurological exam	0.5	↓	BF	NS	NS	p < 0.01 (194)	p < 0.01 (168)	Huisman et al. (1995a)
Bayley Scales of Infant Development								Koopman-Esseboom et al. (1996)
MDI	3	—	BF + FF	NS	NS	NS	NS	
PDI	3	↓	BF + FF	NS	p = 0.02 (198)	NS	NS	
MDI	7	—	BF + FF	NS	NS	NS	NS	
PDI	7	↓	BF + FF	NS	NS	NS	p = 0.05 (182)	
MDI	18	—	BF + FF	NS	NS	NS	NS	
PDI	18	—	BF + FF	NS	NS	NS	NS	
Neurological optimality	18	↓	BF + FF	p = 0.003 (373)	p=0.002 (373)	NS	NS	Huisman et al. (1995b)
Fluency of motility	18	—	BF + FF	NS	NS	NS	NS	Huisman et al. (1995b)
Touwen/Hempel neurological exam	42	—	BF + FF	NS	NS	NS	NS	Lanting et al. (1998)
K-ABC								

Overall cognitive	42	↓	BF + FF	NS	p = 0.005 (373)	NS	NS	Patandin et al. (1999b)
Sequential		↓	BF + FF	NS	p = 0.02 (373)	NS	NS	
Simultaneous		↓	BF + FF	p = 0.02 (384)	p = 0.02 (384)	NS	NS	
Reynell language		—	BF + FF	NS	NS	NS	NS	
K-ABC								
Overall cognitive	42	—	BF	NS	NS	NS	NS	
Sequential		—	BF	NS	NS	NS	NS	
Simultaneous		—	BF	NS	NS	NS	NS	
Reynell language		—	BF	NS	NS	NS	NS	
K-ABC								
Overall cognitive	42	↓	FF	NS	p = 0.0006 (178)	NS	NS	
Sequential		↓	FF	NS	p = 0.002 (178)	NS	NS	
Simultaneous		↓	FF	p = 0.02	p = 0.007 (186)	NS	NS	
Reynell language		↓	FF	p = 0.01	p = 0.03 (90)	NS	NS	

Assessment of a number of functional domains was performed at 3.5 years. Children were tested on the Dutch version of the Kaufman Assessment Battery for Children (K-ABC) and the Reynall Language Development Scales (RDLS) (Patandin *et al*., 1999b). Increased PCB concentration in maternal or cord blood predicted poorer performance on the K-ABC in the formula-fed group only, but not the breast-fed group, despite the fact that PCB levels were higher in breast-feeding mothers and in the children at 3.5 years (Patandin *et al*., 1997). This may be due to the fact that the children from the breast-fed group were from a more socially advantaged environment (Vreugdenhil *et al*., 2002a). Similarly, adverse effects of *in utero* exposure were observed in formula-fed infants but not breast-fed infants on the RLDS. Effects were not related to postnatal exposure or the various measures of TEQ.

Effects on some measures were also found to be related to the concurrent body burden of the child at 3.5 years but not to prenatal exposure as measured by maternal or cord blood PCB concentrations. Significant associations were observed for increased reaction time on a vigilance task, more hyperactive behavior on a parents' questionnaire, and poorer attention in the breast-fed group (Patandin *et al*., 1999c). The fact that these effects were observed in the breast-fed group may reflect the higher body burdens of breast-fed children. Errors of commission on the vigilance task were associated with PCB concentrations in cord blood. TEQ was not associated with any measure.

Problem behavior was assessed at 3.5 years using the Child Behavior Check List (CBCL) (Patandin *et al*., 1999a). Effects were found on the internalizing, withdrawn/depressed scales, and aggressive scales associated with maternal or cord plasma PCB concentrations and/or breast milk TEQ.

The Dutch study found negative effects of PCBs at 6.5 years of age on the McCarthy Scales in less- but not more-advantaged children (Vreugdenhil *et al*., 2002a). Poorer

performance was associated with prenatal exposure as measured by the sum of the four congeners in maternal or cord blood, but not with TEQ or postnatal exposure. Analyses revealed that it was because formula-fed infants were from less advantaged homes, and not the formula-versus-breast-fed dichotomy *per se*, that accounted for the difference in performance on the McCarthy scales.

Sexually dimorphic play behavior was examined at 7.5 years using the Pre-School Activity Inventory to test the hypothesis that PCBs and dioxins exert effects on behavior via endocrine disruption (Vreugdenhil *et al*., 2002b). Prenatal PCB concentrations were associated with less masculinized play behavior in boys and more masculinized behavior in girls, whereas higher prenatal dioxin levels were associated with more feminized play behavior in both boys and girls.

An interesting strategy for the determination of pre- versus postnatal effects was adopted by the Dutch investigators in an assessment of performance on several tasks at 9.0 years of age (Vreugdenhil *et al*., 2004). The half of the cohort from Rotterdam were assessed on the Tower of London, a task that requires planning a number of moves to reach a goal, and measures executive function. Children were also tested on simple reaction time, visuospatial recognition, and auditory memory tasks. Maternal serum PCB concentrations were associated with poorer performance on the Tower of London, and longer and more variable reaction times on the reaction time task (Table 4). In additional analyses, the cohort was divided into six groups: formula-fed, low or high prenatal exposure as assessed by maternal blood levels; breast-fed for less than 16 weeks, low or high prenatal exposure; and breast-fed for more than 16 weeks, low or high prenatal exposure. On the Tower of London, there was evidence of prenatal effects (formula-fed high vs. low) as well as a postnatal effect (breast-fed low vs. formula-fed low). There was a marginal effect of breast-fed long vs. breast-fed short, and other comparisons were as would be expected (breast-fed short or long vs. formula-fed). On a simple reaction-time task, only prenatal exposure was predictive of performance.

Table 4. Summary of the effects of prenatal and postnatal exposure at 9 years in the Dutch study

Variable	ΣPCB_{high} versus ΣPCB_{low} (=0)			BF_{short} versus FF (=0)			BF_{long} versus FF (=0)			BF_{long} versus BF_{short} (=0)			Adjusted R^2
	B	*SE B*	*p*	*B*	*SE B*	*p*	*B*	*SE B*	*p*	*B*	*SE B*	*p*	
Simple reaction time test													
reaction time	26.58	12.76	.041	18.88	13.79	.175	20.42	14.03	.150	1.53	15.70	.922	.04
standard deviation	22.04	6.77	.002	2.48	7.31	.735	-6.95	7.44	.354	-9.44	8.33	.261	.23
Tower of London	-1.85	.67	.007	-.39	.72	.593	-1.81	.73	.015	-1.42	.82	.089	.23

Results for multiple simultaneous regression analysis: FF = formula fed; BF_{short} = 6-16 weeks of breast-feeding; BF_{long} = > 17 weeks of breast-feeding

The Dutch investigators also examined the effects of PCBs on thyroid hormone status of mother and infants, as well as immune status and function. Decreased thyroid hormones and deficits in immune function were observed in this cohort (see Schantz *et al*., 2003, for review). No information is available about the relative sensitivity of these effects compared to

neurotoxicity. However, the effects on cognitive and other behavioral endpoints clearly constitute adverse effects, whereas the consequences of the changes in other organ systems are less clear.

D. German Study

The German study consisted of 171 mother-infant pairs recruited in Düsseldorf in 1993. As in the Dutch study, exposure to PCBs was through the general food supply. The study measured three congeners (153, 138, and 180) in cord plasma and breast milk, and recorded weeks of breastfeeding. Covariates included maternal IQ, parental education, HOME score, smoking and alcohol consumption during pregnancy, mother's body mass index, Apgar score, parity, and health status. Lead concentration was measured in cord blood.

Unlike results for the Michigan and Oswego studies, no effect was observed on the Fagan Test of Recognition Memory at 7 months, perhaps because of poor experimental control (Winneke *et al*., 1998). PCB levels in breast milk were associated with poorer performance on the Bayley MDI at 7 months. Negative associations were also observed for breast milk PCB levels and the Bayley at 30 months and the K-ABC at 42 months after covariate control (Walkowiak *et al*., 2001). HOME score was positively associated with mental and motor development on the Bayley Scales at 30 months and on the K-ABC at 42 months, whereas increasing milk PCB concentrations were associated with poorer performance, when each variable was adjusted for the other (Walkowiak *et al*., 2001). An effect of postnatal exposure was also observed on the K-ABC, as measured both by the child's blood PCB level at 42 months and the breast milk PCB concentration times the weeks of breast feeding, after control for prenatal exposure. Potential effects of postnatal exposure were apparently not assessed before 42 months.

Based on 70 children (fewer than half the original cohort) effects of neither milk PCB levels (prenatal exposure) nor the child's concurrent blood PCB concentration (postnatal exposure) were significantly associated with the K-ABC at 72 months of age, although the trend was negative for both for the mental processing scale (Winneke *et al*., 2002). Effects of the HOME score were still a predictor of positive outcome at 72 months on the K-ABC in this relatively advantaged population (Winneke *et al*., 2002).

E. Faroe Islands Study

The Faroe Islands study was designed to assess the effects of *in utero* methylmercury exposure, with mothers recruited in 1986–1987 (Grandjean *et al*., 1997). Five PCB congeners (118, 138, 153, 170, and 180) were measured in cord tissue in half the cohort only, but only 138, 153, and 180 were used as exposure markers. Covariates included maternal IQ, maternal and paternal education, paternal employment, maternal smoking and alcohol consumption during pregnancy, the child's familiarity with computers and computer games, and other environmental and demographic factors. Methylmercury was measured in maternal hair and umbilical cord blood, and in the child at 1 and 7 years. Concentrations of p,p´-DDE were measured in cord tissue in half the cohort.

Performance was assessed on a number of domain-specific tests at 7 years of age in 917 children. Behavior was not measured before 7 years. Tests included finger tap, a continuous performance (vigilance) task, three subtests of the WISC-R (Digit Spans, Similarities, and Block

Designs), the Bender Visual Motor Test, the California Verbal Learning Test, and the Boston Naming Test.

Only limited effects of PCBs were observed prior to control for methylmercury exposure (Grandjean *et al*., 2001) despite high PCB concentrations in this population (Longnecker *et al*., 2003). A negative association was found between cord tissue PCB levels and performance on the Boston Naming Test, a test of language development, before adjustment for methylmercury. This is consistent with the effects on language in the Dutch and Michigan studies. Effects were also found on reaction time on a continuous performance (vigilance) task. Effects on vigilance task performance were also observed in the Michigan, Dutch, and Oswego studies, but on commission errors (impulse control) rather than reaction time (attention). No effects of PCBs were found on any endpoint in the Faroe Islands study after controlling for methylmercury exposure, although there was some indication of effects on several endpoints in children in the highest tertile with respect to methylmercury. The reason for the lack of results in this study are unknown. A lean tissue (cord tissue) was used for PCB analysis, which might result in less accurate analysis and thereby exposure misclassification. The correlation between cord blood and cord tissue PCB concentrations, based on 50 samples, was 0.90 after log transformation. In the Dutch and German studies, media with higher concentrations of PCBs (maternal blood or milk) were better predictors of performance than cord blood. Cord blood PCB concentrations did not predict performance on any measure in the German study, and on only a few measures in the Dutch study. In the Oswego study, only cord blood concentrations were available, but 68 congeners rather than three were used as measures of exposure. In addition, the more highly-chlorinated congeners best predicted performance, and often total PCBs did not. Finally, the Faroe Islands study only assessed the effects of PCBs at 7 years of age, on endpoints designed to be sensitive to the neurotoxic effects of methylmercury. However, these endpoints assessed some of the domains affected by PCBs in other studies.

F. Summary

These studies are all high quality studies. All have good covariate control for typical (non-chemical) potential confounders. With respect to exposure to chemicals other than PCBs, the studies differed in the completeness of assessment. The Oswego study analyzed a number of chemicals that are found in Lake Ontario fish, including mercury, DDE, mirex, and hexachlorobenzene. Additionally, lead concentrations were determined in the children. The Michigan study was also designed to compare the offspring of fish-eaters versus non-fish-eaters. The study has been criticized for not determining exposure to methylmercury (NRC, 2000), which may have been correlated with PCB levels. The Oswego study was designed in many ways as a replication of the Michigan study, and effects were similar even after controlling for methylmercury. The major difference between the studies is the disappearance of effects on IQ in the Oswego study later in childhood; however, the PCB levels in the Oswego study were lower than those in the Michigan study. Neither the Dutch nor German study were designed to assess the effects of exposure to PCBs through fish; exposure was assumed to be through the general food supply. In fact, the Dutch investigators estimated that fish contributed 11% and dairy products contributed 43% of the PCB-TEQ body burden in preschool children (Patandin *et al*., 1999d). There is no reason to believe that PCBs and methylmercury body burdens would be highly correlated in either the Dutch or German study. The Faroe Islands study analyzed PCBs

and DDE in cord tissue in addition to methylmercury. Lead was apparently not measured in either the Dutch or Faroe Islands studies, but would not be expected to be correlated with PCBs.

There is reasonable congruence among the various studies with respect to the pattern of neurotoxic effects, perhaps with the exception of the Faroe Islands study (Table 1). All the studies that examined neurological function during infancy identified effects of prenatal PCB exposure. Effects on IQ were identified in early childhood in all studies. Deficits in IQ and other cognitive endpoints were still apparent at 11 years in the Michigan study. In the Dutch study, IQ deficits only persisted in less advantaged children. The Michigan study also found that children of less intellectually competent mothers exhibited deficits at 4 and 11 years, whereas more advantaged children did not. In the Oswego and German studies, the effects on IQ were attenuated or not present later in childhood. This was also true in the Faroe Islands study on the three subtests of full-scale IQ that were assessed. The Faroe Islands study did not find effects on attention and language, identified in the Michigan study. The Michigan, Dutch, and Oswego studies also assessed behavioral domains in addition to IQ. All three found adverse effects on a number of endpoints at the oldest ages tested, which are indicative of deficits in executive function. This suggests that developmental PCB exposure has permanent effects on the ability to plan and exercise impulse control. It also suggests that standard clinical measures of IQ are not as sensitive in detecting deficits produced by PCB exposure as more domain-specific tasks. It further indicates that although the effects on IQ attenuate or disappear at later ages, deficits in important cognitive domains persist. A number of other behavioral domains were also found to be affected in the Dutch study.

IV. Body Burden of PCBs in Epidemiological Studies and the U.S. Population

Comparison of exposures among epidemiological studies is not straightforward for several reasons. The Michigan study used older, less sensitive analytical methodology that did not determine concentrations of individual congeners. Newer studies analyzed different congeners and different numbers of congeners. In addition, PCBs were assayed in different tissues (cord blood, maternal blood, breast milk, cord tissue), with some studies measuring levels in more than one tissue.

The Dutch investigators reported the concentration of four congeners in maternal and cord plasma, breast milk, and the children's blood at 3.5 years (Koopman-Esseboom *et al*., 1994; Patandin *et al*., 1997) (Table 5). Higher PCB blood concentrations at 3.5 years were observed in the breast-fed infants as a consequence of breast-feeding.

Table 5. Mean PCB Plasma Level (ug/L)

	118	138	153	180
maternal blood	0.15	0.56	0.84	0.50
cord blood	0.04	0.11	0.15	0.08
child 3.5 yr				
breast-fed	0.06	0.20	0.33	0.16
formula-fed	0.03	0.06	0.08	0.04

For the German study, the cord blood PCB levels, based on congeners 138, 153, and 180, were 0.28, 0.33, and 0.50 ug/L for the 25th, 50th, and 75th percentiles, respectively (Walkowiak *et al*., 2001). Based on comparison of the levels for the three congeners measured in the German study, exposures in the German and Dutch study were similar (median 0.33 and 0.34 ug/L for the German and Dutch studies, respectively). These congeners are the most prevalent in human tissue, and would be expected to constitute about 50–60% of the total PCB levels.

The Oswego study did not report concentrations for individual congeners in their publications. Total PCB cord blood levels, based on 68 congeners, were 0.174, 25th percentile; 0.525, 50th percentile; and 1.11 ng/g wet weight, 75th percentile (Stewart *et al*., 2000).

The PCB congener typically present at highest concentration in human tissue is PCB 153 (a non-dioxin like congener). The correlation between congeners 153 and other congeners is typically substantial. For example, in the Faroe Islands study, the correlation coefficient between congener 153 and the other congeners measured in cord tissue (118, 138, 170, and 180) was 0.73–0.92, with the correlation for the sum being 0.99 (Grandjean *et al*., 2001). In a study in the Arctic, PCB congeners were measured in cord blood and the child's blood (Després *et al*., 2005). Correlation coefficients between cord blood 153 concentrations and congeners 99, 118, 138, 170, 180, or 187 were 0.84–0.98, with the coefficient for the sum being 0.96. For the child's blood, correlations were 0.91–0.99 for the same congeners plus 156, with the overall correlation coefficient being 0.98.

The 5th, 25th, 50th, 75th, and 95th percentiles of congener 153 were estimated in maternal serum across a number of studies, including the studies described above (Longnecker *et al*., 2003). The Dutch, German, and Oswego studies measured congener 153 directly in cord blood, maternal blood, and/or breast milk. The Faroe Islands study measured congener 153 in cord tissue. The Michigan study investigators quantified 14 congeners in a subset of blood samples, including 153. The ratio of this value to the original values determined by packed column was used to estimate concentrations of congener 153 for the entire cohort. Based on this analysis, the Michigan, Dutch, and German studies were comparable in terms of exposures. Median maternal serum concentrations were estimated to be 120 ng/g lipid in the Michigan study, 100 ng/g lipid in the Dutch study, and 140 ng/g lipid in the German study. Maternal serum concentrations in the Faroe Islands study were estimated to be much higher: 450 ng/g lipid. Exposures in the Oswego study were lower than in the other studies. The median lipid-adjusted maternal serum

congener 153 concentration in the Oswego study was estimated to be 40 ng/g, the 5th percentile was about 10 ng/g, and the 95th percentile was about 120 ng/g.

The NHANES survey measured a number of PCB congeners in blood beginning in 1999. Data for 1999-2000 for women of reproductive age are available on the CDC Web site. The 95th percentile for congener 153 was 122 ng/g, similar to that observed in the Oswego study. Unfortunately, the analytical methodology used by CDC was relatively insensitive, so that the median is expressed as <29 ng/g (lipid adjusted). Nonetheless, it appears that the range of exposures in the Oswego study is similar to that in the U.S. as a whole.

V. Evidence for Relative Neurotoxicity of Individual Congeners

The relative toxicity of dioxin-like versus non-dioxin-like congeners with respect to neurotoxicity is unknown. The Oswego study did not analyze the planar congeners (77, 126, and 169). Dioxin-like congeners 118, 105, 170, and 180 were measured. Results have not been published comparing the predictive power of dioxin-like versus non-dioxin-like congeners. However, in the Oswego study, the sum of the most highly chlorinated congeners best predicted performance.

The study that is the most informative with respect to the relative toxicity of congeners is the Dutch study. The Dutch study measured the dioxin-like congeners 77, 126, 169, 105, 118, 110, 67, 77, and 180 in breast milk only, and 118 and 180 in cord and maternal blood. They also measured a number of dioxins and furans, and combined the TEFs in various ways to assess the effects of different TEQs. Congener 126 is the most active with respect to Ah receptor activation, which does not seem to be an important mechanism for neurotoxicity. For cognitive effects, maternal blood PCB levels were the best predictors of performance measures on the Bayley Scales during infancy (Koopman-Esseboom *et al*., 1996), and the K-ABC at 3.5 years of age (Patandin *et al*., 1999b). The sum of PCBs in cord blood was predictive of five outcomes, whereas maternal blood PCB levels were predictive of nine outcomes. This may well be due to the higher levels in maternal compared to cord blood, allowing more accurate measurement of PCB concentrations. PCB levels in milk and milk TEQ were both predictive of only one measure in early assessments: neurological status during infancy (Huisman *et al*., 1995; Koopman-Esseboom *et al*., 1996). Similarly, planar, mono-ortho, or dioxin TEQ were not predictive of free play behavior, performance on a vigilance task, or activity according to a parents' questionnaire at 3.5 years (Patandin *et al*., 1999d). Total TEQ, dioxin-TEQ, and planar PCB TEQ were each predictive of a more adverse score on the internalizing scale of the CBCL, whereas the sum of the four congeners measured in maternal or cord blood were not (Patandin *et al*., 1999a). All measures were predictive of adverse scores on the withdrawal/depressed scale. In a subsequent study on play behavior, all four measures were predictive of differential behavior in boys and girls: dioxin TEQ in milk predicted more feminized play behavior in both sexes, whereas the sum of the four PCB congeners in cord or maternal blood predicted less masculinized behavior in boys and the sum of the four PCB congeners in milk predicted more masculinized behavior in girls (Vreugdenhil *et al*., 2002).

The behavioral effects of *in utero* and lactational exposure to individual congeners has been studied for only a few congeners in animal studies, and some have only been assessed in a single study (Rice, 2004). In a series of studies in rats with dioxin (TCDD) and five PCB congeners with or without dioxin-like properties (28, 118, 153, 77, 95), Schantz and colleagues

(Schantz *et al*., 1996, 1997, 1995) found all to be neurotoxic, but with different patterns of impairment on the two tasks examined. There was no pattern in terms of the relative potencies of dioxin-like versus non-dioxin-like congeners in that series of studies, with most PCB congeners having LOAEL/NOAELs within an order of magnitude of each other. Congener 126 had a LOAEL four orders of magnitude lower than the other congeners tested by Schantz and colleagues, with PCB-treated rats making fewer errors than controls. Rice and colleagues (Bushnell and Rice, 1999; Crofton and Rice, 1999; Geller *et al*., 2000; Rice and Hayward, 1999; Rice, 1999), on the other hand, reported minimal neurotoxicity following developmental exposure to congener 126 on a variety of tests of cognition and sensory function, at the same doses used by Schantz and colleagues and a longer exposure time. Effects were observed in other organ systems (weight gain, anogenital distance, blood biochemistry, thyroid hormones) in the cohort. Effects of postnatal exposure to congeners 156 and 52 have been assessed in the mouse. However, the results are difficult to interpret since littermates were treated as independent observations in the statistical analysis, a serious violation of experimental design.

In the Dutch study, the breast milk concentration of 153 was 186 ng/g lipid, and the concentration of 126 was 0.152 ng/g lipid, three orders of magnitude less. The concentration of the second most potent Ah receptor activator, 169, was 0.0843 ng/g. The total concentrations of non-dioxin-like PCBs in breast milk was 455.9 ng/g, and the sum of planar PCBs was 0.2556 ng/g. The sum in breast milk of 118, 138, 153, and 180, the congeners also measured in cord and maternal blood, was about 428 ng/g. These results are consistent with those from other studies on body congener patterns of PCBs in human tissues. Even if the planar PCBs were particularly toxic, the total concentration is so low that they would not contribute significantly to the overall toxicity.

The issue of which congeners are producing toxicity is an important one for public health. It appears from the Dutch study that TEQ in breast milk did not predict performance on most outcome measures early in life, but then neither did non-dioxin-like congeners in breast milk. Cognitive effects, including deficits on IQ, were best predicted by maternal PCB concentrations as measured by the four congeners analyzed in maternal blood. TEQ was predictive of outcome on non-cognitive endpoints at 3.5 years of age, and on the masculine/feminine dimension of play behavior at 6.5 years. The Oswego study measured a reasonable number of congeners, but did not include most dioxin-like PCBs, including the most potent congeners, 126 and 169; therefore there is not the opportunity to determine whether TEQ is predictive of performance. In the Oswego study, the more highly chlorinated PCBs best predicted performance, but that may be because these congeners are more reliably analyzed than lower-chlorinated congeners because of lack of interference from other chemicals. Both the German and Faroe Islands studies used only three congeners as markers of exposure. The question of whether some congeners are more toxic than others, and which those may be, remains largely unaddressed in either epidemioloigcal or whole animal studies.

VI. Determination of the relationship between exposure and effect

There is no information published to date on the shape of the relationship between exposure of the infant (or child) to PCBs and performance on any measure. It is unknown whether the relationship is best fit by a linear model, which would suggest that there is no threshold within the range of body burdens studied, or whether it is sublinear (shallower slope at lower body burdens), suggesting that there is a threshold of body burden below which there does

not appear to be an adverse effect. This is of vital importance to our understanding of the potential burden for society that ubiquitous exposure to PCBs may produce. Investigators of these studies performed analyses to determine whether there was a statistical association between exposure and performance on one or more measures, which is the standard form of analysis. In contrast to PCBs, the shape of the exposure-effect relationship, and whether there may be a threshold, has been studied for the neurotoxicants lead and methylmercury, both by individual investigators (Davidson *et al*., 2001; Canfield *et al*., 2003; Bellinger and Needleman, 2003) and government agencies (NRC, 2000; Budtz-Jørgensen *et al*., 1999, 2000; Schwartz 1994). For those neurotoxicants, there is evidence that the relationship may be supralinear: i.e., a relatively steeper slope, and therefore greater relative effect, at lower body burdens than at higher. The shape of the dose-effect relationship for PCBs, however, is unclear.

Some limited information may be gleaned from graphic representation of data in publications. For example, in the Dutch study, performance on the K-ABC was represented graphically in five categories (Patandin *et al*., 1999b). For all scores (overall cognitive, sequential processing, and simultaneous processing), all four of the higher groups performed more poorly than the lowest group (sum PCB in maternal plasma < 1.5 ppb, Fig 5). Information is not available concerning performance in the lowest category, so no conclusions may be drawn concerning possible threshold. Similarly, there appears to be a more-or-less monotonic relationship in the Oswego study between increased PCB cord blood levels (those with values below the limit of detection, compared to other groups) for performance on the McCarthy General Cognitive Index, Perceptual and Quantitative Scales (Stewart *et al*., 2003, Fig. 1) and errors of commission on a vigilance task at 9.5 years of age (Stewart *et al*., 2005, Fig. 2). In the German study, the second quintile with respect to PCB milk levels appears unimpaired relative to the lowest quintile on the Bayley Scales at 30 or 42 months (Walkowiak *et al*., 2001, Fig. 1), suggestive of a threshold. Such ad hoc divination by the reader of course is thoroughly inadequate in determining the association between body burden and effect.

The Michigan investigators performed a Bench Mark Dose (BMD) analysis of four outcomes measured at 11 years of age (Jacobson *et al*., 2002b). This analysis is useful for risk assessment, in that it calculates an exposure (body burden) associated with a defined risk, which can then serve as the starting point for deriving an acceptable intake level. The issue of the shape of the exposure-effect relationship was not explored, however: a linear relationship was apparently assumed. For p0 = 0.05 and BMR = 0.05 (the values used for the methylmercury assessment), BMDLs were 0.63-0.71 ug/g or 630 to 710 ng/g. This BMD analysis could provide a starting point for derivation of an RfD based on human data. BMD analyses have also been performed for IQ at 3.5 years of age from the Dutch and German study for EPA, but the results have not been made public.

The Oswego study may provide the best data for a hazard assessment of PCBs noncarcinogenic effects, since it is the most recent U.S. study, and over 60 PCB congeners were measured, (Stewart *et al*., 1999) rather than just a few (Huisman *et al*., 1995; Winneke *et al*., 1998) or an estimate based on Aroclor analysis (Jacobson and Jacobson, 1993). Exposures measured in the Oswego study were the lowest of these recent studies (based on levels of congener 153). In addition, data are available from the Oswego study on fish intake by the mother and PCB concentration in Lake Ontario fish (Lonky *et al*., 1996).

Hazard analyses based on the Oswego (or other epidemiological) studies would ideally be based on benchmark dose (BMD) analysis of the relationship between body burden (maternal and/or cord blood) and effect on various endpoints. To derive an RfD, a pharmacokinetic model of some sort would have to be used to convert from body burden to maternal intake.

VII. Recommendation for Development of a Striped Bass/Bluefish Advisory

The epidemiological studies have documented robust behavioral deficits resulting from *in utero* exposure to PCBs. Based on the Oswego study, deleterious effects appear to occur at body burdens typical of women in the general U.S. population.

PCBs have a long half-life in the human body, decades for some congeners. Therefore exposure across the lifespan, including during childhood, determines transgeneration exposure. This is also the case for dioxins; it was because of this reality that the National Academy of Sciences Institute of Medicine recommended that exposure be minimized, beginning in early childhood (IOM, 2003). Current levels of exposure may already be within the range associated with adverse developmental outcomes. Consequently it is recommended that any advisory for striped bass and bluefish not result in an appreciable increase in the body burden of PCBs for females. Based upon studies in the Dutch population (Patandin, et al., 1999) it appears that fish consumption constitutes a relatively small proportion (approx. 10%) of PCB exposure. The goal of a body burden approach for striped bass advisories would be to make sure that the dietary percentage from fish and thus the overall PCB dose does not appreciably increase.

This recommendation is a departure from the standard risk-based approaches involving an RfD or CSF to determine limits of exposure and in some ways can be more complex. Setting a fish consumption limit based upon background body burden may involve one of three approaches (or a combination of the 3) as follows.

1) The recommendation could be based on an estimation of the potential contribution to body burden of US women from consumption of a particular fish species. This requires knowledge of the fish PCB concentration (mean, median, percentiles), the fish ingestion rate (this variable can be backfit to derive the target daily dose), and a toxicokinetic tool (e.g., PBTK model) to convert daily dose in mg/kg/d to body burden. This tool would be similar to the biokinetic slope factor used in lead risk assessment modeling. The population distribution of toxicant body burden would be derived from actual biomonitoring data or from modeling approaches. The incremental increase in body burden due to PCBs in striped bass would then be estimated using dosimetry modeling approaches. The acceptable increment in body burden due to striped bass would be a risk management decision. While this analytical option may be the most robust, it requires data and techniques not currently available for PCBs (e.g., biokinetic model). Further, using this approach for PCBs is more complicated than for lead due to the large number of congeners that would need to be considered in modeling PCB body burden. These congeners will each have their own biokinetics and toxicological properties.

2) Rather than base decisions on body burden, it may be more direct to consider background daily dose of PCBs in the U.S. diet and to have as a goal that the

fish species in question contribute no more than a certain percentage to total daily PCB dose. This approach necessitates knowledge of PCB levels in commonly eaten foods and distributional inputs for the level of consumption of these foods. These dietary calculations have been conducted for dioxins. Some data regarding PCBs in food items exist, with several studies providing calculations of PCB dietary intake in the general population (Newsome, et al., 1998; Zuccato, et al., 1999; Patandin, et al., 1999; Focant, et al., 2002; Llobet, et al., 2003). This dataset is limited in that there is not much information for the U.S. and that it is not up-to-date. Based upon the very small number of samples in FDA's Total Dietary Survey (TDS) (http://www.cfsan.fda.gov/~acrobat/tds1byps.pdf), PCBs do not appear to be an important target analyte for FDA. The international studies (Canada, Holland, Spain, Belgium, Italy) are mixed in reporting total PCBs vs. PCBs as dioxin toxicity equivalents (TEQs) and thus do not provide a unified dataset of PCB dietary exposure. Of most relevance to fish consumption advisories is the dietary exposure to total PCBs since that is how PCBs are most frequently analyzed in fish. The datasets available for the U.S. (Schechter, et al., 2001; Judd, et al., 2004) focus on dioxin TEQs rather than total PCBs. The limited calculations that are available for dietary exposure to total PCBs shows a wide range, 1-10 ug/d in Italy (Zuccato, et al., 1999) and 0.4 ug/d in Canada (Newsome, et al., 1998). These data can provide a general framework for striped bass meal frequency considerations or one can attempt to work with PCBs data reported as dioxin TEQs (e.g., Schechter, et al., 2001; Judd, et al., 2004; Patandin, et al., 1999). In either case, additional dietary data are needed to solidify this approach.

3) The third approach also uses background exposure rates in foods as a point of comparison, except that this approach is less comprehensive than #2 above. In this case, the acceptability of a given bass ingestion rate would be judged against other PCB-containing foods that are commonly eaten and for which there are no special precautions. There would be no cumulation of exposure dose, just direct comparisons of dose from striped bass to dose from other specific food items. This approach may be the simplest in that data on PCB levels in dairy, meat, poultry, etc. can be obtained, consumption rates can be found in tables, and the daily PCB dose from these items can be compared to what may be available from striped bass. It would then be assumed that a consumption rate of striped bass which contributed no more daily dose than what is available in these other commonly eaten food items, would also not substantially increase body burden. Issues would arise as to which PCB fish concentration to use as the basis of calculations (mean, median, upper percentile), as well as the consumption rate that should be used for the comparison foods.

Alternatively, the typical RfD/CSF approach could be used for girls and women of childbearing potential. In this case, a hazard assessment should be performed for both cancer and non-cancer effects. The current EPA cancer slope factor of 2 mg/kg/day should be used as the basis for the cancer assessment, with a 10^{-5} cancer risk. For noncancer effects, the RfD for 1254 is appropriate. The same RfD and CSF should be used for derivation of an advisory for males and females without reproduction potential.

References

Bellinger, D.C. Effect modification in epidemiologic studies of low-level neurotoxicant exposures and health outcomes. Neurotoxicol Teratol 2000; 22:133-140.

Bellinger, D.C., and Needleman, H.L. Intellectual impairment and blood lead levels. New Eng J Med 2003; 349:500-502.

Budtz-Jørgensen, E., Keiding, N., and Grandjean, P. Benchmark modeling of the Faroese methylmercury data. Final Report to U.S. EPA. Research Report 99/5. Copenhagen: Department of Biostatistics, University of Copenhagen, 1999.

Budtz-Jørgensen, E., Grandjean, P., Keiding, N., et al. Benchmark dose calculations of methylmercury-associated neurobehavioral deficits. Toxicol Lett 2000; 112-113:193-199.

Bushnell, P.J., and Rice, D.C. Behavioral assessments of learning and attention in rats exposed perinatally to 3,3',4,4',5-pentachlorobiphenyl (PCB 126). Neurotoxicol Teratol 1999; 21:381-392.

Canfield, R.L., Henderson, C.R., Cory-Slechta, D.A., Cox, C., Jusko, T.A., and Lanphear, B.P. Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. New Eng J Med 2003; 348:1517-1526.

Cordle, F., Locke, R., and Springer, J.. Risk assessment in a Federal regulatory agency: An assessment of risk associated with the human consumption of some species of fish contaminanted with polychlorinated biphenyls (PCBs). Environ Health Perspect 1982; 45:171-182.

Crofton, K.M., and Rice, D.C. Low-frequency hearing loss following perinatal exposure to 3,3',4,4',5-pentachlorobiphenyl (PCB 126) in rats. Neurotoxicol Teratol 1999; 21:299-301.

Darvill, T., Lonky, E., Reihman, J., Stewart, P., and Pagano, J. Prenatal exposure to PCBs and infant performance on the Fagan Test of Infant Intelligence. Neurotoxicol 2000; 21:1029-1038.

Davidson, P.W., Kost, J., Myers, G.J., Cox, C., Clarkson, T.W., and Shamlaye, C.F. Methylmercury and neurodevelopment: Reanalysis of the Seychelles Child Development Study outcomes at 66 months of age. JAMA 2001; 285:1291-1293.

Després, C., Beuter, A., Richer, F., Poitras, K., Veilleux, A., Ayotte, P., Dewailly, É., Saint-Amour, D., and Muckle, G. Neuromotor functions in Inuit preschool children exposed to Pb, PCBs, and Hg. Neurotoxicol Teratol 2005; 27:245-257.

Fein, G.G., Jacobson, J.L., Jacobson, S.W., Schwartz, P.M., and Dowler, M.A. Prenatal exposure to polychlorinated biphenyls: Effects on birth size and gestational age. J Pediatr 1984; 105:315-320.

Focant, JF, Eppe, G., Pirard, C., Massart, AC, Andre, JE and De Pauw, E. Levels and congener distributions of PCDDs, PCDFs and non-ortho PCBs in Belgian foodstuffs – assessment of dietary intake. Chemosphere 2002: 48: 167-179.

Geller, A.M., Bushnell, P.J., and Rice, D.C. Behavioral and electrophysiological estimates of visual thresholds in awake rats treated with 3,3',4,4',5-pentachlorobiphenyl (PCB 126). Neurotoxicol Teratol 2000; 22:521-531.

GLSFATF (Great Lakes Sport Fish Advisory Task Force). Protocol for a uniform Great Lakes sport fish consumption advisory. 1993; p. 81.

Grandjean, P., Weihe, P., Burse, V.W., Needham, L.L., Storr-Hansen, E., Heinzow, B., Debes, F., Murata, K., Simonsen, H., Ellefsen, P., Budtz-Jørgensen, E., Keiding, N., & White, R.F. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. Neurotoxicol. Teratol.2001; 23, 305–317.

Grandjean, P., Weihe, P., White, R., Debes, F., Arak, S., Yokoyama, K., Murata, K., Sorensen, N., Dahl, R., and Jorgensen P. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 1997; 20:1-12.

Grandjean, P., Weihe, P., Burse, V.W., Needham, L.L., Storr-Hansen, E., Heinzow, B., Debes, F., Murata, K., Simonsen, H., Ellefsen, P., Budtz-Jørgensen, E., Keiding, N., and White, R.F. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. Neurotoxicol Teratol 2001; 23:305-317.

Huisman, M., Koopman-Esseboom, C., Fidler, V., Hadders-Algra, M., van der Paauw, C.G., Tuinstra, L.G.M.Th., Weisglas-Kuperus, N., Sauer, P.J.J., Touwen, B.C.L., and Boersma, E.R. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Hum Devel 1995a; 41:111-127.

Huisman, M., Koopman-Esseboom, C., Lanting, C.I., van der Paauw, C.G., Tuinstra, L.G., Fidler, V., Weisglas-Kuperus, N., Sauer, P.J., Boersma, E.R., Touwen, B.C. Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. Early Hum Dev 1995b; 43:165-76.

IOM (Institute of Medicine). Dioxins and Dioxin-Like Compounds in the Food Supply: Strategies to Decrease Exposure. Washington, DC: National Academies Press. 2003. http://www.nap.edu/

Jacobson, J.L., and Jacobson, S.W. A 4-year follow-up study of children born to consumers of Lake Michigan fish. J. Great Lakes Res. 1993; 19:776-783.

Jacobson, J. L., and Jacobson, S.W. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. New Eng J Med 1996; 335:783-789.

Jacobson, J.L., and Jacobson SW. Breastfeeding and gender as moderators of teratogenic effects on cognitive development. Neurotoxicol Teratol 2002a; 24:349-358.

Jacobson, J.L., and Jacobson, S.W. Specific effects of prenatal PCB exposure on attention and behavior in school-age children. XX International Neurotoxicology Meeting, Little Rock AR, Feb 9-12, 2003a.

Jacobson, J.L., and Jacobson, S.W. Prenatal exposure to polychlorinated biphenyls and attention at school age. J Pediatr 2003b; 143:780-788.

Jacobson, J.L., Jacobson, S.W., Fein, G.G., Schwartz, P.M., and Dowler, J.K. Prenatal exposure to an environmental toxin: A test of the multiple effects model. Dev Psychol 1984; 20:523-532.

Jacobson, J.L., Jacobson, S.W., and Humphrey, H.E.B. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J Pediatr 1990a; 116:38-45.

Jacobson, J.L., Jacobson, S.W., and Humphrey, H.E.B. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotoxicol Teratol 1990b; 12:319-326.

Jacobson, J.L., Jacobson, S.W., Padgett, R.J., Brummit, G.A., & Billings, R.L. Effects of prenatal PCB exposure on cognitive processing efficiency and sustained attention. Dev Psychol 1992; 28:297-306.

Jacobson, J.L., Janisse, J., Banerjee, M., Jester, J., Jacobson, S.W., and Ager, J.W. A benchmark dose analysis of prenatal exposure to polychlorinated biphenyls. Environ Health Perspect 2002b; 110:393-398.

Jacobson, S.W., Chiodo, L.M., and Jacobson, J.L. Breastfeeding effects on intelligence quotient in 4- and 11-year-old children. Pediatr 1999; 103:e71-e77.

Jacobson, S.W., Fein, G.G., Jacobson, J.L., Schwartz, P.M., and Dowler, J.K. The effect of intrauterine PCB exposure on visual recognition memory. Child Devel 1985; 56:853-860.

Jacobson, S.W., and Jacobson, J.L. Breastfeeding and intelligence. Lancet 1992; 339:926.

Judd, N., Griffith, W.C. and Faustman, E.M. (2004) Contribution of PCB exposure from fish consumption to total dioxin-like dietary exposure. Reg. Toxicol. Pharmacol. 2004: 40: 125-135.

Koopman-Esseboom C, Huisman M, Weisglas-Kuperus N, Van der Paauw C, Tuinstra L, Boersma E, et al. PCB and dioxin levels in plasma and human milk of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant's exposure to PCBs and dioxins. Chemosphere 1994; 28:1721-1732.

Koopman-Esseboom, C., Weisglas-Kuperus, N., de Ridder, M.A.J., van der Paauw, C.G., Tuinstra, L.G.M.Th., and Sauer, P.J.J. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatr 1996; 97:700-706.

Lanting, C.I., Patandin, S., Fidler, V., Weisglas-Kuperus, N., Sauer, P.J.J., Boersma, E.R., et al. Neurological condition in 42-month-old children in relation to pre- and postnatal exposure to polychlorinated biphenyls and dioxins. Early Hum Dev 1998; 50:283–292.

Llobet, J.M., Bocio, A., Domingo, J.L., Teixido, A., Casas, C. and Muller, L. Levels of polychlorinated biphenyls in foods from Catalonia, Spain: estimated dietary intake. J Food Prot 2003: 66: 479-484.

Longnecker, M.P., Wolff, M.S., Gladen, B.C., Brock, J.W., Grandjean, P., Jacobson, J.L., Korrick, S.A., Rogan, W.J., Weisglas-Kuperus, N., Hertz-Picciotto, I., Ayotte, P., Stewart, P., Winneke, G., Charles, M.J., Jacobson, S.W., Dewailly, E., Boersma, E.R., Altshul, L.M., Heinzow, B., Pagano, J.J., and Jensen, A.A. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Environ Health Perspect 2003; 111:65-70.

Lonky, E., Reihman, J., Darvill, T., Mather, J. Sr., and Daly, H. Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J Great Lakes Res 1996; 22:198-212.

Minnesota DOH (Minnesota Department of Health). PCB Reference Dose for Effects on Fetal Development: Development of a reference dose based on human exposure data. HRA series 92-FSH-002, 1992.

Newsome, WH, Davies, DJ and Sun, WF. Residues of polychlorinated biphenyls (PCB) in fatty foods of the Canadian diet. Food Addit Contam. 1998: 15: 19-29.

NRC (National Research Council). Toxicological Effects of Methylmercury. Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council. Washington, DC: National Academy Press, 2000.

Patandin, S., Weisglas-Kuperus, N., de Ridder, M.A.J., Koopman-Esseboom, C., van Staveren, W.A., van der Pauuw, C.G., and Sauer, P.J.J. Plasma polychlorinated biphenyl levels in

Dutch preschool children either breast-fed or formula-fed during infancy. Am J Pub Health 1997; 87:1711-1714.

Patandin, S., Koopman-Esseboom, C., De Ridder, M.A.J., Weisglas-Kuperus, N., and Sauer, P.J.J. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. Pediatr Res 1998; 44:538–545.

Patantin, S., Koot, H.M., Sauer, P.J.J., and Weisglas-Kuperus, N. Problem behavior in Dutch preschool children in relation to background polychlorinated biphenyl and dioxin exposure. In: Effects of environmental exposure to polychlorinated biphenyls and dioxins on growth and development in young children. Ph.D. thesis. Erasmus University, Rotterdam, 1999a; 143-156.

Patandin, S., Lanting, C.I., Mulder, P.G.H., Boersma, E.R., Sauer, P.J.J., and Weisglas-Kuperus, N. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 1999b; 134:33-41.

Patandin, S., Veenstra, J., Mulder, P.G.H., Sewnaik, A., Sauer, P.J.J., and Weisglas-Kuperus, N. Attention and activity in 42-month-old Dutch children with environmental exposure to polychlorinated biphenyls and dioxins. In: Effects of environmental exposure to polychlorinated biphenyls and dioxins on growth and development in young children. Ph.D. thesis. Erasmus University, Rotterdam, 1999c; 123-142.

Patandin, S., Dagnelie, P.C., Mulder, P.G., Op de Coul, E., van der Veen, J.E., Weisglas-Kuperus, N., and Sauer, P.J. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: A comparison between breastfeeding, toddler, and long-term exposure. Environ Health Perspect 1999d; 107:45-51.

Rice, D.C. Effect of exposure to 3,3',4,4',5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on development and spatial delayed alternation performance in rats. Neurotoxicol Teratol 1999; 21:59-69.

Rice, D.C. Comparison of Potencies of Individual PCB Congeners on Non-Cancer Endpoints in Animal Studies. Prepared for the European Food Safety Authority (EFSA), Commitment #FSA 734; 2004.

Rice, D.C. Developmental PCB exposure on neuropsycholoical function in epidemiological studies: Issues and research needs, in Human Developmental Neurotoxicology, edited by D.C. Bellinger, New York: Marcel Dekker Press, 2006.

Rice, D.C., and Hayward, S. Effects of exposure to 3,3',4,4',5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on behavior (concurrent random interval-random interval and progressive ratio performance) in rats. Neurotoxicol Teratol 1999; 21:679-687.

Schantz, S.L., Moshtaghian, J., and Ness D.K. Spatial learning deficits in adult rats exposed to ortho-substituted PCB congeners during gestation and lactation. Fundam Appl Toxicol 1995; 26:117-126.

Schantz, S.L., Seo, B.W., Moshtaghian, J., Peterson, R.E., and Moore, R.W. Effects of gestational and lactational exposure to TCDD or coplanar PCBs on spatial learning. Neurotoxicol Teratol 1996; 18:305-313.

Schantz, S.L., Seo, B.W., Wong, P.W., and Pessah, I.N. Long-term effects of developmental exposure to 2,2´,3,5´,6-pentachlorobiphenyl (PCB 95) on locomotor activity, spatial learning and memory and brain ryanodine binding. Neurotoxicol 1997; 18:457-468.

Schantz, S.L., Widholm, J.J., and Rice, D.C. Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect 2003; 111:357-376.

Schecter, A., Cramer, P., Boggess, K., Stanley, J., Papke, O., Olson, J. Silver, A. and Schmitz, M. Intake of dioxins and related compounds from food in the U.S. population. J Toxicol Environ Health 2001: 63: 1-18.

Schwartz, J. Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ Res 1994; 65:42-55.

Stewart, P., Darvill, T., Lonky, E., Reihman, J., Pagano, J., and Bush, B. Assessment of prenatal exposure to PCBs from maternal consumption of Great Lakes fish: An analysis of PCB pattern and concentration. Environ Res Section A 1999; 80:S87-S96.

Stewart, P., Fitzgerald, B., Reihman, J., Gump, B., Lonky, E., Darvill, T., Pagano, J., and Hansen, P. Prenatal PCB exposure, the corpus collosum, and response inhibition. Environ Health Perspect 2003a; 111:1670-1677.

Stewart, P., Reihman, J., Gump, B., Lonky, E., Darvill, T., and Pagano, J. Response inhibition at 8 and 9 ½ years of age in children prenatally exposed to PCBs. Neurotoxicol Teratol 2005; 27:771-780.

Stewart, P.W., Reihman, J., Lonky, E.I., Darvil, T.J., and Pagano, J. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. Neurotoxicol Teratol 2003b; 25:1–12.

Stewart, P., Reihman, J., Lonky, E., Darvill, T., and Pagano, J. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. Neurotoxicol Teratol 2000; 22:21-29.

Tilson, H. A., J. L. Jacobson, and W. J. Rogan. Polychlorinated biphenyls and the developing nervous system: cross-species comparisons. Neurotoxicol Teratol 1990; 12:239-248.

Vreugdenhil, H.J.I., Lanting, C.I., Mulder, P.G.H., Boersma, R., and Weisglas-Kuperus, N. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J Pediatr 2002a; 140:48-56.

Vreugdenhil, H.J., Mulder, P.G., Emmen, H.H., and Weisglas-Kuperus, N. Effects of perinatal exposure to PCBs on neuropsychological functions in the Rotterdam cohort at 9 years of age. Neuropsychol 2004; 18:185-193.

Vreugdenhil, H.J.I., Slijper, F.M.E., Mulder, P.G.H., and Weisglas-Kuperus, N. Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age. Environ Health Perspect 2002b; 110:A593–A598.

Walkowiak, J., Wiener, J.-A., Fastabend, A., Heinzow, B., Schmidt, E., Steingruber, H.-J., Wundram, S., and Winneke, G. Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. Lancet 2001; 358:1602-1607.

Winneke, G., Bucholski, A., Heinzow, B., Kraemer, U., Schmidt, E., Walkowiak, J., Wiener, J.-A., and Steingruber, H.-J. Developmental neurotoxicity of polychlorinated biphenyls (PCBs): Cognitive and psychomotor functions in 7-month old children. Toxicol Lett 1998; 102–103:423–428.

Winneke, G., Kraemer, U., Walkowiak, J., Fastabend, A., Heinzow, B., Borte, M., Herbarth, O., Steingruber, H.-J. Delay of neurobehavioral development following pre- and postnatal PCB exposure: Persistent or reversible? The Second PCB Workshop — Recent advances in the environmental toxicology and health effects of PCBs. Brno, Czech Republic, May 2002. Abstract published in Naunyn-Schmiedeberg's Arch Pharmacol 2002; Vol. 365 supplement, Hedelberg: Springer-Verlag.

Zuccato, E., Calvarese, S., Mariani, G., Mangiapan, S., Grasso, P., Guzzi, A., Fanelli, R. Level sources and toxicity of polychlorinated biphenyls in the Italian diet. Chemosphere 1999: 38: 2753-2765.